NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 456

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (CAS NO. 147-47-7) IN F344/N RATS AND B6C3F$_1$ MICE (DERMAL STUDIES)

AND THE

INITIATION/PROMOTION (DERMAL STUDY) IN FEMALE SENCAR MICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE
(CAS NO. 147-47-7)

IN F344/N RATS AND B6C3F$_1$ MICE
(DERMAL STUDIES)

AND THE

INITIATION/PROMOTION STUDY
(DERMAL STUDY)

IN FEMALE SENCAR MICE

NATIONAL TOXICOLOGY PROGRAM
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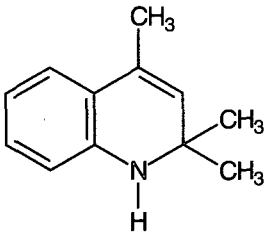
CONTENTS

ABSTRACT



1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MONOMER)

CAS No. 147-47-7

Chemical Formula: $C_{12}H_{15}N$ Molecular Weight: 173.28

Synonyms: 2,2,4-Trimethyl-1,2-dihydroquinoline; acetone anil; methylquinoline
Trade names: Agerite Resin D; Flectol A; Flectol H; Flectol Pastilles; Vulkanox HS/LG; Vulkanox HS/Powder

1,2-Dihydro-2,2,4-trimethylquinoline (monomer) is used as an antioxidant in styrene-butadiene and nitrile-butadiene rubbers and latexes. It was nominated by the National Cancer Institute as part of a review of chemicals used in the manufacture and processing of rubber, during which potential occupational and consumer exposure to this compound can occur. It was selected for evaluation because it is a derivative of quinoline, a known rodent carcinogen, and was regarded as having potential carcinogenic activity. Because of the pattern of use and exposure, dermal administration was considered most appropriate.

Male and female F344/N rats and B6C3F$_1$ mice received topical applications of 1,2-dihydro-2,2,4-trimethylquinoline in acetone (greater than 90% pure) for 13 weeks or 2 years. Groups of female SENCAR mice received 1,2-dihydro-2,2,4-trimethylquinoline (greater than 90% pure) during a 1-year dermal initiation/promotion study to determine the tumor initiation or promotion potential of the chemical. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood cells.

13-Week Study in Rats

Groups of 10 male and 10 female F344/N rats were topically administered 0, 5, 20, 50, 100, or 200 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 13 weeks. In addition, there were 10 male and 10 female untreated controls. All rats survived to the end of the study. Final mean body weights and mean body weight gains of treated male and female rats were similar to those of the vehicle controls except those of 200 mg/kg males, which were significantly lower than those of the vehicle controls. The only notable clinical observation was skin discoloration of treated rats. In the 200 mg/kg groups, absolute and relative liver weights of males and absolute liver weights of females were significantly greater than those of the vehicle controls. There were no significant differences in hematology or clinical chemistry parameters, reproductive tissue parameters, or estrous cycle characterization between treated and control groups. Histopathologic lesions of the skin at the site of application included acanthosis and hyperkeratosis in 100 and 200 mg/kg males and 200 mg/kg females. Cytoplasmic vacuolization of hepatocytes of mild tomoderate severity was observed

in the livers of all 200 mg/kg males and was considered treatment related. Based on the incidence and severity of skin and liver lesions observed in 200 mg/kg rats in the 13-week study, 100 mg/kg was selected as the high dose for the 2-year rat study.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were topically administered 0, 2.5, 5, 10, 20, or 50 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 13 weeks. In addition, there were 10 male and 10 female untreated controls. All mice except one 2.5 mg/kg female survived to the end of the study. Final mean body weights and mean body weight gains of male and female mice were similar to those of the vehicle controls. There were no treatment-related clinical observations. There were no significant differences between treated and control groups in organ weights, hematology, and clinical chemistry parameters, reproductive tissue parameters, or estrous cycle characterization. Histopathologic lesions of the skin at the site of application included acanthosis (epidermal hyperplasia), hyperkeratosis, and parakeratosis, all ranging from minimal to mild in severity. Minimal to mild fibrosis and subchronic inflammation were observed in the dermis. Based on the incidences and severities of skin lesions observed in 20 and 50 mg/kg mice in the 13-week study, 10 mg/kg was selected as the high dose for the 2-year mouse study.

2-YEAR STUDY IN RATS

Groups of 60 male and 60 female F344/N rats were topically administered 0, 36, 60, or 100 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 103 (males) or 104 (females) weeks. Ten rats per group were evaluated after 15 months of treatment.

Survival and Body Weights

Survival of treated rats was similar to that of controls. Mean body weights of 60 mg/kg males and 100 mg/kg males and females were slightly lower than those of the controls after week 21. Mean body weights of 36 mg/kg males and females and 60 mg/kg females were generally similar to those of the controls throughout the study.

Pathology Findings

No skin neoplasms were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline. Several nonneoplastic skin lesions were determined to be treatment related. Incidences of acanthosis at the site of application in all treated groups of males and in 100 mg/kg females at the 15-month interim evaluation were significantly greater than those in the controls. At the end of the 2-year study, incidences of acanthosis at the site of application in 60 and 100 mg/kg males and females and hyperkeratosis at the site of application in 60 mg/kg females were significantly greater than those in the controls. Absolute and relative right kidney weights of 60 and 100 mg/kg male rats were significantly greater than those of the controls at the 15-month interim evaluation. Incidences of renal tubule adenoma and adenoma or carcinoma (combined) in all treated groups of males were significantly greater than those in the controls. These incidences exceeded the range from the historical controls in 2-year NTP feed studies. An extended (step section) evaluation of the kidneys of male rats did not reveal an additional increase in neoplastic response because additional adenomas and hyperplasias were observed in the controls as well as in treated groups.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female B6C3F$_1$ mice were topically administered 0, 3.6, 6, or 10 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 103 (males) or 104 (females) weeks. Nine or ten mice per group were evaluated after 15 months of treatment.

Survival and Body Weights

Survival of treated mice was similar to that of controls. Mean body weights of treated male and female mice were similar to those of the controls throughout the study.

Pathology Findings

No neoplasms or nonneoplastic lesions were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline.

1-Year Initiation/Promotion Study in Female SENCAR Mice

Groups of 30 female SENCAR mice were topically administered varying initiation/promotion treatments as outlined in the table below.

Survival, Body Weights, and Clinical Findings

Survival in all treated groups was similar to that of the respective controls, except in the 2.5 µg 7,12-dimethylbenz(a)anthracene (DMBA)/0.5 µg 12-*O*-tetradecanoylphorbol-13-acetate (TPA) group in which survival was significantly lower than that of the controls. Mean body weights of all treated groups were similar to those of the respective controls throughout the study. No clinical observations were associated with 1,2-dihydro-2,2,4-trimethylquinoline treatment; however, mice promoted with TPA showed signs of irritation and papilloma at the site of application.

Pathology Findings

Initiation and promotion with acetone alone was not associated with any skin lesions at the site of application. The incidences of acanthosis and chronic inflammation were increased in all groups promoted with TPA regardless of the initiator treatment; however, the incidences of nonneoplastic lesions were low in all other groups. Incidences of squamous cell papillomas and squamous cell carcinomas were markedly increased in the DMBA/TPA positive control group; however, no response was observed in groups initiated with DMBA and promoted with 5, 10, or 25 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline or in the group initiated with 1,2-dihydro-2,2,4-trimethylquinoline and promoted with TPA.

Design of the 1-Year Initiation/Promotion Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline in Female SENCAR Mice[a]

Treatment[b]		
Initiator[c]	**Promoter[d]**	**Treatment Group**
Acetone	Acetone[e]	Vehicle Control
2.5 µg DMBA	Acetone	DMBA Initiation Control
Acetone	0.5 µg TPA[f]	TPA Promotion Control
2.5 µg DMBA	0.5 µg TPA	Initiation/Promotion Control
50 mg/kg TMQ	0.5 µg TPA	TMQ Initiation
2.5 µg DMBA	5 mg/kg TMQ[g]	TMQ Promotion
2.5 µg DMBA	10 mg/kg TMQ	TMQ Promotion
2.5 µg DMBA	25 mg/kg TMQ	TMQ Promotion
Acetone	5 mg/kg TMQ	TMQ Promotion Control
Acetone	10 mg/kg TMQ	TMQ Promotion Control
Acetone	25 mg/kg TMQ	TMQ Promotion Control

[a] Thirty mice per treatment group
[b] DMBA = 7,12-dimethylbenz(a)anthracene; TPA = 12-*O*-tetradecanoylphorbol-13-acetate; TMQ = 1,2-dihydro-2,2,4-trimethylquinoline
[c] Initiators were applied once during week 1 of the study in a volume of 0.1 mL.
[d] Promoters were applied in a volume of 0.1 mL
[e] Acetone promotion: three times per week
[f] TPA promotion: one time per week
[g] 1,2-Dihydro-2,2,4-trimethylquinoline promotion: three times per week

GENETIC TOXICOLOGY

1,2-Dihydro-2,2,4-trimethylquinoline was not mutagenic in any of several strains of *Salmonella typhimurium*, with or without S9 metabolic activation. 1,2-Dihydro-2,2,4-trimethylquinoline induced sister chromatid exchanges in cultured Chinese hamster ovary cells in the absence of S9, but not in the presence of S9. However, no increase in the frequency of chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with 1,2-dihydro-2,2,4-trimethylquinoline, with or without S9. No increase in the frequency of micronucleated erythrocytes was noted in peripheral blood of male or female mice exposed topically to 1,2-dihydro-2,2,4-trimethylquinoline for 13 weeks.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *some evidence of carcinogenic activity** of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats, based on increased incidences of renal tubule adenoma and adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of 1,2-dihydro-2,2,4-trimethylquinoline in female F344/N rats receiving 36, 60, or 100 mg/kg, or in male or female B6C3F$_1$ mice receiving 3.6, 6, or 10 mg/kg.

Exposure of rats to 1,2-dihydro-2,2,4-trimethylquinoline by dermal application in acetone for 2 years resulted in acanthosis in males and females and hyperkeratosis in females at the site of application. No nonneoplastic lesions in male or female mice were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 1,2-Dihydro-2,2,4-trimethylquinoline

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 36, 60, or 100 mg/kg applied topically in acetone	0, 36, 60, or 100 mg/kg applied topically in acetone	0, 3.6, 6, or 10 mg/kg applied topically in acetone	0, 3.6, 6, or 10 mg/kg applied topically in acetone
Body weights	60 and 100 mg/kg groups slightly lower than controls	100 mg/kg group slightly lower than controls	Treated groups similar to controls	Treated groups similar to controls
2-Year survival rates	5/50, 2/50, 4/50, 1/50	19/50, 21/50, 22/50, 22/50	39/50, 37/50, 41/50, 37/50	34/50, 40/50, 40/51, 40/50
Nonneoplastic effects	Skin (site of application): acanthosis (1/50, 4/50, 14/49, 21/50)	Skin (site of application): acanthosis (0/50, 1/50, 9/50, 22/50); hyperkeratosis (0/50, 1/50, 7/50, 1/50)	None	None
Neoplastic effects	Kidney: renal tubule adenoma (standard evaluation — 1/50, 7/50, 10/50, 7/50; extended evaluation — 6/50, 5/50, 6/50, 8/50; standard and extended evaluations — 7/50, 11/50, 14/50, 14/50); renal tubule adenoma or carcinoma (standard evaluation — 1/50, 8/50, 10/50, 7/50; extended evaluation — 6/50, 6/50, 6/50, 8/50; standard and extended evaluations — 7/50, 12/50, 14/50, 14/50)	None	None	None
Level of evidence of carcinogenic activity	Some evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; positive without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (I) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 1,2-dihydro-2,2,4-trimethylquinoline on June 20, 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 20, 1995, the draft Technical Report on the toxicology and carcinogenesis studies of 1,2-dihydro-2,2,4-trimethylquinoline received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of 1,2-dihydro-2,2,4-trimethylquinoline by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in male rats and nonneoplastic lesions in male and female rats. The proposed conclusions were *some evidence of carcinogenic activity* of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats and *no evidence of carcinogenic activity* in female F344/N rats or in male or female B6C3F$_1$ mice.

Dr. Irwin summarized the results of the 1-year initiation/promotion study in female SENCAR mice. He said that 1,2-dihydro-2,2,4-trimethylquinoline did not promote 7,12-dimethylbenz(a)anthracene-initiated skin, while 12-*O*-tetradecanoylphorbol-13-acetate did not promote 1,2-dihydro-2,2,4-trimethylquinoline-initiated skin in SENCAR mice. Thus, in this system, 1,2-dihydro-2,2,4-trimethylquinoline did not behave as either an initiator or a promoter.

Dr. Karol, a principal reviewer, agreed with the proposed conclusions. She noted that survival of both control and treated male rats was reduced from that of females by week 90.

Dr. Ryan, the second principal reviewer, did not fully agree with the proposed conclusions in male mice where she would have supported "equivocal" or even "some evidence of carcinogenic activity." She asked if it were not premature to use the Seilkop method to discount the dose effect on liver neoplasms in male mice, since the procedure used to adjust for weight effects on neoplasm incidence may not be broadly enough accepted at this point. Dr. J.K. Haseman, NIEHS, said that although Seilkop's logistic regression model was relatively new, it had provided an excellent fit to individual neoplasm and body weight data from over 3,500 animals in the NTP historical control database. Dr. Ryan asked whether it would be possible to use a dose response model to decide on dose levels for the chronic study, based on the short-term studies, focusing her concern on why an intermediate dose between 50 and 100 mg/kg was not chosen as the high dose for female rats in the 2-year study. Dr. Irwin responded that doses intermediate to those in the prechronic study are frequently picked. However, the consensus for this study was that the 100 mg/kg dose for rats did not produce a severe enough reaction of the skin to worry about in terms of the 2-year study.

Dr. Ward, the third principal reviewer, agreed with the proposed conclusions. He noted that the incidence rate for combined liver neoplasms in 10 mg/kg male mice exceeded the historical control range for both feed and dermal studies, but agreed it was probably reasonable to discount them after adjusting for weight effects on neoplasm incidence. Dr. Irwin said body weight was not the only factor, but also lack of nonneoplastic liver lesions in males and the lack of supporting neoplastic lesions in female mice entered into the interpretation. Dr. Ward said another discussion point was that the incidences of liver neoplasms were similar in high and low dose groups, and there were no increases in neoplasm multiplicity or incidences of foci. Dr. Goldsworthy said he was unconvinced that increases in liver foci had been ruled out in male mice. Dr. M. Stevens, Monsanto, commented that in his experience with short-term and long-term studies with other quinolines, the liver was the target organ.

Dr. Ward moved that the Technical Report on 1,2-dihydro-2,2,4-trimethylquinoline be accepted with the revisions discussed and with the conclusions as written for male rats, *some evidence of carcinogenic activity*, and for female rats and male and female mice, *no evidence of carcinogenic activity*. Dr. Miller seconded the motion, which was accepted with seven yes votes and one abstention (Dr. Goldsworthy, who said he lacked enough information on the liver response in male mice to dismiss a higher level of evidence).